Highly potent and selective RET inhibitor, BLU-667, achieves proof of concept in ARROW, a phase 1 study of advanced, RET-altered solid tumors

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- AbbVie Inc
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- National Cancer Institute-Cancer Therapy Evaluation Program

BLU-667 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines)
Receptor tyrosine kinase, **RE**arranged during **Transfection** (**RET**)

Normal RET signaling

- **GDNF ligand**
- **GFRα1**
- **TK1**
- **TK2**

RET Receptor Tyrosine Kinase

RAS/RAF/MEK/ERK

Organ development and tissue homeostasis

 ✓
Receptor tyrosine kinase, \textbf{RE}arranged during Transfection (\textit{RET})

Activating \textit{RET} \textbf{mutations}:

- C620/C634
- Dimeric \textit{RET} \textbf{fusions}:
  - KIF5B-, CCDC6-, NCOA4, TRIM-33- and more partners

\textbf{RET} \textbf{Proto-oncogene}

\textbf{GDNF ligand}

\textbf{RAS/RAF/MEK/ERK}

\textbf{Organ development and tissue homeostasis}

\textbf{Tumorigenesis}

Normal \textbf{RET} \textbf{signaling}

Oncogenic \textbf{RET} \textbf{signaling}
 RET is a rare driver of multiple, diverse tumor types\textsuperscript{1,2}

- Medullary thyroid cancer: >60% \textit{RET}-mutations
- Papillary thyroid cancer: \textasciitilde{}10% \textit{RET}-fusions
- Non-small cell lung cancer: \textasciitilde{}1-2% \textit{RET}-fusions

- Esophageal cancer
- Breast cancer
- Melanoma
- Colorectal cancer
- Leukemia

Other tumor types \leq{}1% \textit{RET}-altered

Patients with *RET*-alterations have not benefited from precision oncology

**Precision oncology**

Non-small cell lung cancer

EGFR mutation  ALK-fusion  ROS-fusion

Selective RTK inhibitors¹
↑Activity and ↓off-target toxicity

**Typical ORR >60%**
**Typical PFS >9 months**
**Favorable tolerability**

MKI, multikinase inhibitors; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; RTK, receptor tyrosine kinase

Patients with *RET*-alterations have not benefited from precision oncology

### Precision oncology

<table>
<thead>
<tr>
<th>Non-small cell lung cancer</th>
<th>NSCLC</th>
<th>MTC</th>
<th>Refractory solid tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR mutation</strong></td>
<td>RET-fusion</td>
<td>RET-mutation</td>
<td>RET-fusion</td>
</tr>
<tr>
<td><strong>ALK-fusion</strong></td>
<td>Chemotherapy</td>
<td>Immunotherapy</td>
<td>Multikinase inhibitors</td>
</tr>
<tr>
<td><strong>ROS-fusion</strong></td>
<td>Multikinase inhibitors</td>
<td>Multikinase inhibitors</td>
<td>No standard of care</td>
</tr>
</tbody>
</table>

#### Selective RTK inhibitors

↑Activity and ↓off-target toxicity

Typical ORR >60%
Typical PFS >9 months
Favorable tolerability

#### Current “non-targeted” paradigms for RET

**Multikinase Inhibitors**

↓Activity and ↑off-target toxicity

- **NSCLC**
  - Typical ORR <30%
  - Typical PFS ~4.6 – 7.3 months
  - MKI have frequent dose reduction/interruption for treatment related toxicity

- **MTC**
  - Typical ORR 25-45%
  - Typical PFS ~11-30 months

MKI, multikinase inhibitors; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; RTK, receptor tyrosine kinase

BLU-667 was designed to treat RET-altered cancers

Subnanomolar potency

<table>
<thead>
<tr>
<th>Variant</th>
<th>Biochemical IC\textsubscript{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET wildtype</td>
<td>0.4</td>
</tr>
<tr>
<td>RET V804L</td>
<td>0.3</td>
</tr>
<tr>
<td>RET V804M</td>
<td>0.4</td>
</tr>
<tr>
<td>RET M918T</td>
<td>0.4</td>
</tr>
<tr>
<td>CCDC6-RET</td>
<td>0.4</td>
</tr>
</tbody>
</table>

More Potent than MKI

Kinome selectivity for RET

![Kinome illustration](image)

<table>
<thead>
<tr>
<th>Variant</th>
<th>More Active than BLU-667</th>
<th>Less Active than BLU-667</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT RET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RET V804L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RET V804M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RET M918T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCDC6 RET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGFR-2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RXDX-105, Vandetanib, Cabozantinib

1. Subbiah V et al. Cancer Discovery April 15 2018

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (CSTI) ([www.cellsignal.com](http://www.cellsignal.com)). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.
BLU-667 potently inhibits RET-driven tumor growth

**KIF5B-RET NSCLC patient-derived xenograft**

- **Graph:**
  - **X-axis:** Days after start of treatment
  - **Y-axis:** Tumor volume (mm$^3$)
  - **Lines:**
    - Vehicle
    - 3 mg/kg BID
    - 10 mg/kg BID
    - 30 mg/kg BID
    - 60 mg/kg QD

**Potent Pathway inhibition**

- **Bar chart:**
  - Percentage reduction in DUSP6/SPRY4 vs vehicle
  - 0% to -100%

**Legend:**
- **BID:** two times per day; **QD:** once daily

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BLU-667 ARROW first-in-human study

**Part 1: Dose escalation – completed**

Opened March 2017

Advanced RET-altered solid tumors
- BOIN design
- BLU-667 orally QD continuous

MTD

**Part 2: Dose expansion – enrolling**

- NSCLC
  - Failed prior kinase inhibitor
- NSCLC
  - No prior kinase inhibitor
- Medullary Thyroid Cancer
- Other RET-altered solid tumors

**Key objectives**

- MTD, safety, pharmacokinetics, pharmacodynamics, anti-tumor activity

BOIN, Bayesian optimal interval; MTD, maximum tolerated dose
### Demography and baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; median (range)</td>
<td>56 (19-83)</td>
</tr>
<tr>
<td>Sex, male; n (%)</td>
<td>30 (57)</td>
</tr>
<tr>
<td>ECOG PS; n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21 (40)</td>
</tr>
<tr>
<td>1</td>
<td>32 (60)</td>
</tr>
<tr>
<td>Metastatic disease; n (%)</td>
<td>50 (94)</td>
</tr>
<tr>
<td>Tumor type; n (%)</td>
<td></td>
</tr>
<tr>
<td><em>RET</em>-alteration</td>
<td>51 (96)</td>
</tr>
<tr>
<td>Medullary thyroid cancer</td>
<td>29 (55)</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>19 (36)</td>
</tr>
<tr>
<td>Papillary thyroid cancer</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Retroperitoneal Paraganglioma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Non-<em>RET</em> altered solid tumor</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior systemic therapy; n (%)</td>
<td>41 (77)</td>
</tr>
<tr>
<td>Multikinase inhibitor; n (%)</td>
<td>27 (51)</td>
</tr>
<tr>
<td>Chemotherapy; n (%)</td>
<td>19 (36)</td>
</tr>
<tr>
<td>Immunotherapy; n (%)</td>
<td>18 (34)</td>
</tr>
<tr>
<td># of lines, median (range)</td>
<td>1 (0-8)</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance score

Data cut-off: April 6, 2018
Diverse RET genotypes enrolled

- **Medullary thyroid cancer** N=29
  - M918T 72%
  - Other RET 10%
  - Multiple 7%
  - V804M 4%
  - C634R 7%

- **KIAA 1468** 5%
  - RET FISH+ 11%

- **Non-small cell lung cancer** N=19
  - CCDC6 21%
  - KIF5B 63%

- **Paraganglioma** N=1
  - RET R77H

- **Papillary thyroid cancer** N=2
  - CCDC6-RET 100%

Data cut-off: April 6, 2018
# Dose escalation results

## Maximum Tolerated Dose – 400 mg QD

<table>
<thead>
<tr>
<th>Dose (mg QD)</th>
<th># Evaluable (N=49)</th>
<th>Dose limiting toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>60</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>100</td>
<td>5</td>
<td>Alanine transaminase increased (1)</td>
</tr>
<tr>
<td>200</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>300</td>
<td>11</td>
<td>Tumor lysis syndrome (1) Hypertension (1)</td>
</tr>
<tr>
<td><strong>400</strong></td>
<td><strong>10</strong></td>
<td>Asthenia (1) Hypertension (1)</td>
</tr>
<tr>
<td>600</td>
<td>4</td>
<td>Hyponatremia (1) Hypertension (1)</td>
</tr>
</tbody>
</table>

**41 of 53 patients remain on treatment (median 3.9 months [range: 0.3–11.5])**

ALT, alanine aminotransferase

Data cut-off: April 6, 2018
Dose-dependent exposure and RET pathway inhibition

**Steady-state Pharmacokinetics**

- BLU-667 mean plasma concentration (ng/mL)
- Time (h)

**Tumor Pharmacodynamics**

- Percentage reduction in DUSP6 and SPRY4 vs Baseline

- BLU-667 mean plasma concentration (ng/mL)
- Time (h)

**Dosages**

- 30 mg QD
- 60 mg QD
- 100 mg QD
- 200 mg QD
- 300 mg QD
- 400 mg QD
- 600 mg QD

**Graphs**

- **Steady-state Pharmacokinetics**
  - Brain IC$_{90}$
  - Plasma IC$_{90}$

- **Tumor Pharmacodynamics**
  - RET → MEK → ERK → DUSP6 / SPRY4
Dose-dependent decline in MTC tumor markers

Carcinoembryonic antigen (CEA)

Calcitonin

Data cut-off: April 6, 2018
Potent activity against highly invasive RET-mutant MTC

27-year-old male; RET L629-D361 Del; initiated at 60 mg; ongoing at 400 mg with confirmed PR
Potent activity against KIF5B-RET NSCLC – post chemotherapy

Baseline

Month 4

FISH

Breakpoint

KIF5B
10p11.22

10q11.21

RET

KIF5B Exons 1-15
Chr10:32315000

Exons 12-20
Chr10:43610000

Reduction in Tumor

cy DNA (% Baseline)

37-year-old female; ongoing at 400 mg with confirmed PR

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0 30 60 90 120 150 180 210 240 270 300

0 1 2 3 4 5 6 7 8 9

0% 20% 40% 60% 80% 100%

-40% -30% -20% -10% 0%
Potent activity against KIF5B-RET NSCLC – post-vandetinib+everolimus

Baseline

First Assessment (Month 2)

74-year-old male; initiated at 300 mg; ongoing at 400 mg; PR at month 5 pending confirmation

Subbiah V et al. Cancer Discovery April 15 2018
Activity against KIF5B-RET NSCLC brain metastases

69-year-old male; initiated at 400 mg; ongoing at month 4

Images courtesy of Drs. of Gainor, J and Lin, J of MGH
BLU-667 has broad anti-tumor activity against RET-altered cancers

Maximum Reduction from Baseline (%)

Best Response | Evaluable Patients (N=40) n, (%)
--- | ---
CR* | 1 (3)
PR** | 17 (43)
SD | 20 (50)
PD | 2 (5)

* confirmed ** 10 confirmed, 7 pending confirmation

C, prior chemotherapy; CR, complete response; I, prior immunotherapy; M, prior MKI therapy; MKI, multikinase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease

Data cut-off: April 6, 2018
BLU-667 has durable activity and high response rate in RET-altered NSCLC

Prior Therapy

Treatment Duration (days)

Best Response | Evaluable Patients (N=14); n (%) |
--- | --- |
CR | 0 |
PR* | 7 (50) |
SD | 5 (36) |
PD | 2 (14) |

* 5 confirmed, 2 pending confirmation

Data cut-off: April 6, 2018

Treatment duration:
Median 3.9 months
Range 0.4–11.4 months
13/19 (68%) on treatment
BLU-667 has durable activity and high response rate in RET-altered MTC

Prior Therapy

Best Response | Evaluable Patients; (N=25) N (%)
---|---
CR* | 1 (4)
PR** | 9 (36)
SD | 15 (60)
PD | 0

*confirmed;**5 confirmed, 4 pending confirmation

Data cut-off: April 6, 2018

Treatment duration:
Median 4.7 months
Range 0.5–11.5 months
25/29 (86%) on treatment
BLU-667 is well tolerated

Treatment-emergent Adverse Events ≥10% per CTCAE
(30-400 mg Safety Population, N=49)

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>10 (20)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>10 (20)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>8 (16)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>4 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (10)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>6 (12)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>6 (12)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (10)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5 (10)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (10)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Most adverse events were Grade 1

8 (16%) patients had Grade 3 treatment-related AE

No Grade 4/5 treatment-related AEs

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events

Data cut-off: April 6, 2018
Conclusions

• **BLU-667 delivers:**
  – Potent RET pathway inhibition with favorable tolerability
  – Broad anti-tumor activity regardless of RET genotype, indication and prior therapy
  – High preliminary response rates and durable activity
    – ORR: RET-fusion NSCLC 50%
    – ORR: RET-mutant MTC 40%
    – ORR: RET-fusions and mutations (NSCLC, MTC and PTC) 45%
    – 41 of 51 RET-altered patients remain on treatment

• **ARROW** dose escalation data validate BLU-667 as a promising precision therapy for RET-altered cancers

• **ARROW** dose expansion is open and enrolling globally

• **BLU-667** manuscript published today in Cancer Discovery
  – Foundational preclinical work and clinical translation

Data cut-off: April 6, 2018
We thank the participating patients, their families, all study co-investigators, and research co-ordinators at the following institutions:

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- Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, United States
- Chao Family Comprehensive Cancer Center University of California Irvine Medical Center, United States
- Abramson Cancer Center, University Of Pennsylvania, United States
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